

Embolotherapy for Neuroendocrine Tumor Liver Metastases: Prognostic Factors for Hepatic Progression-Free Survival and Overall Survival



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Background

- Optimal embolotherapy for neuroendocrine tumor (NET) liver metastases remains controversial due to limited outcomes data, resulting in wide practice variations.
- Purpose: To evaluate the impact of disease and treatment related factors on survival outcomes following embolotherapy.

Methods

- Multicenter retrospective study of 150 patients with NET liver metastases from gut, pancreas, bronchial, or other primary sites treated with conventional transarterial chemoembolization (TACE), transarterial radioembolization (TARE), or transarterial embolization (TAE) between 2004-2015. Indications for embolotherapy were tumor progression (67%), symptoms (18%), tumor burden (11%), downstaging (3%), or other (1%).
- Survival endpoints were hepatic progression-free survival (HPFS) and overall survival (OS). Survival analyses were performed using Kaplan-Meier estimate as well as univariate and multivariate Cox proportional hazards models.

Demographics

	TACE (n=47)	TARE (n=62)	TAE (n=41)	P-value
Age Mean (SD)	58 (13) yrs	62 (11) yrs	59 (9) yrs	0.19
Sex Male	28 (60%)	37 (60%)	20 (49%)	0.49
Tumor grade				0.001
1 (n = 74)	14 (30%)	31 (50%)	29 (71%)	
2 (n = 56)	21 (45%)	24 (39%)	11 (27%)	
3 (n = 20)	12 (25%)	7 (11%)	1 (2%)	
Tumor burden				0.39
< 25%	19 (40%)	27 (44%)	16 (39%)	
25 - 50%	16 (34%)	24 (39%)	10 (24%)	
50 - 75%	8 (17%)	7 (11%)	12 (29%)	
> 75%	4 (9%)	4 (6%)	3 (7%)	
Tumor primary site				0.61
Pancreatic (n = 67)	21 (45%)	24 (49%)	22 (54%)	
Gut (n = 68)	22 (47%)	30 (48%)	16 (39%)	
Bronchial (n = 8)	3 (6%)	3 (5%)	2 (5%)	
Other (n = 7)	1 (2%)	5 (8%)	1 (2%)	
Extrahepatic metastases	23 (49%)	28 (45%)	28 (68%)	0.06
Systemic therapy				
Octreotide	35 (74%)	48 (77%)	34 (83%)	0.63
Biologic	10 (21%)	15 (24%)	10 (24%)	0.92
Cytotoxic	12 (26%)	23 (37%)	14 (34%)	0.43
Prior hepatic resection or ablation	13 (28%)	13 (21%)	8 (20%)	0.61

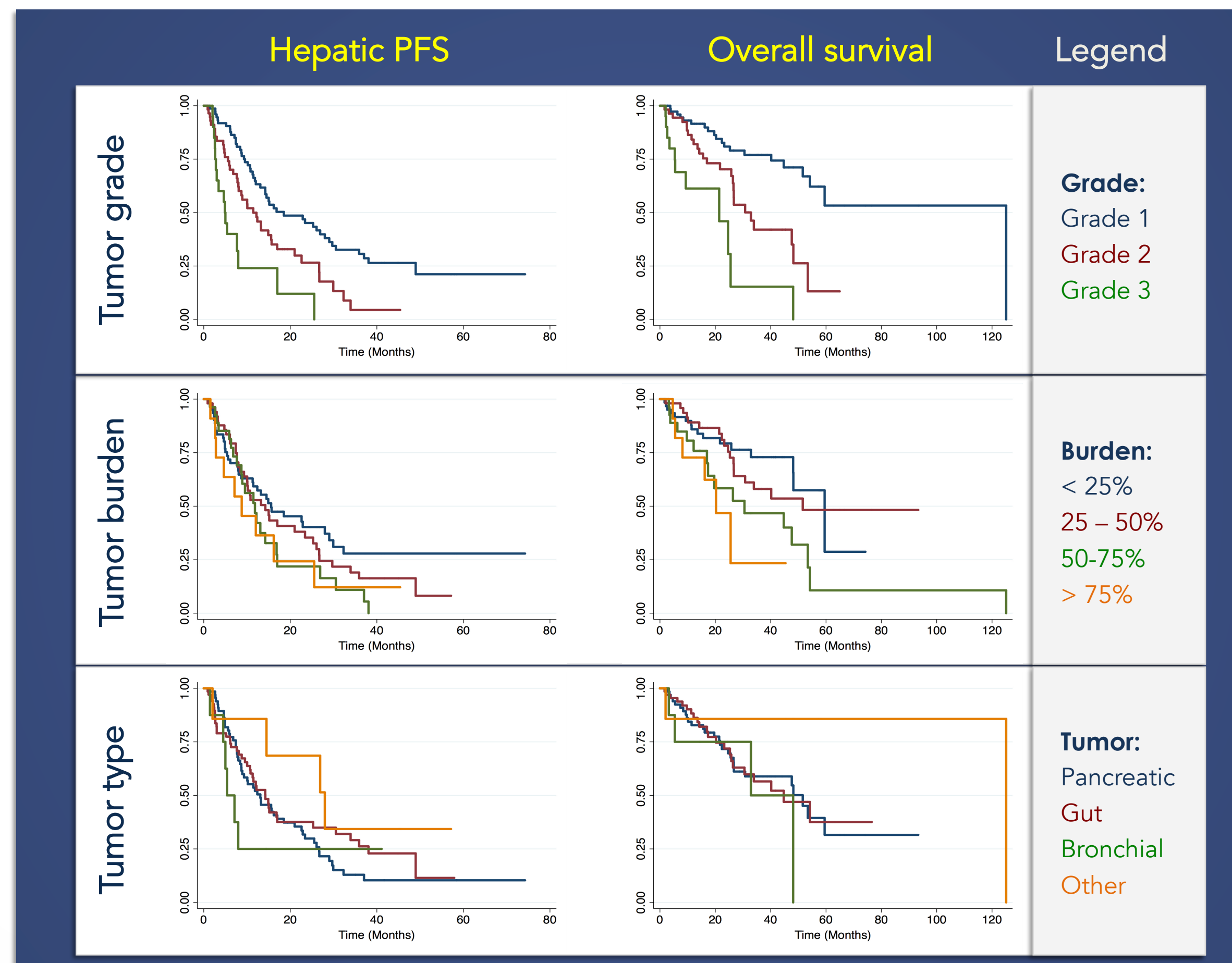
Results

- Median follow-up time was 22 months (range: 2 – 125 months).
- Disease-related factors:**
 - Higher tumor grade and hepatic tumor burden reduced time to HPFS and OS failure.
 - No significant differences in HPFS or OS were seen among gut, pancreas, or lung primaries.
- Treatment-related factors:**
 - In multivariate analysis, there was an interaction between embolization technique and tumor grade.
 - In grade 1 and 2 tumors, TARE demonstrated 17.7 and 7.6 month longer median HPFS versus TACE respectively ($p < 0.05$). In grade 3 tumors, TARE demonstrated 1.6 month shorter median HPFS ($p = 0.09$) and 22.1 month shorter median OS versus TACE ($p < 0.005$).
 - HPFS and OS after TAE were not significantly different from TACE and TARE in multivariate analysis.
 - HPFS and OS were not significantly different between yttrium-90 microsphere agents (glass vs. resin) or TACE chemotherapy regimens (doxorubicin alone vs. combination with mitomycin C and/or cisplatin).

Survival Analysis: Cox Models

	Hepatic PFS			Overall survival		
	Median HPFS (months)	Uni-variate HR	Multi-variate HR	Median OS (months)	Uni-variate HR	Multi-variate HR
Tumor grade						
1 (n=74)	18.5	1	1	125.1	1	1
2 (n=56)	11.4	1.89**	1.99	32.9	2.83*	1.72
3 (n=20)	4.9	4.32**	1.43	21.4	7.60**	1.92
Tumor burden						
< 25% (n=62)	15.6	1	1	59.5	1	1
25-50% (n=50)	14.2	1.24	1.69*	51.6	1.20	1.56
50-75% (n=27)	11.8	1.66	2.32*	30.5	2.38*	3.50*
> 75% (n=11)	8.8	1.78	2.99*	20.3	3.30*	5.08**
Tumor primary site						
Pancreatic (n=67)	13.1	1	1	51.6	1	1
Gut (n=68)	14.2	0.84	1.12	44.7	1.00	1.85
Bronchial (n=8)	5.4	1.41	1.31	32.9	1.52	0.69
Other (n=7)	28.0	0.47	0.40	125.1	0.23	0.20
Extrahepatic mets (n=94)	14.9	0.88	0.81	51.6	0.94	1.04
Embolotherapy						
Grade 1						
TACE (n=14)	8.4	1	1	59.5	1	1
TARE (n=32)	26.1	0.47*	0.47*	N/A	0.73	0.53
TAE (n=30)	15.1	0.66	0.61	N/A	0.56	0.34
Grade 2						
TACE (n=25)	8.1	1	1	30.8	1	1
TARE (n=25)	15.7	0.43*	0.41*	33.9	0.90	0.73
TAE (n=12)	10.0	0.49	0.55	26.4	1.23	1.17
Grade 3						
TACE (n=13)	5.0	1	1	25.5	1	1
TARE (n=7)	3.4	2.56	4.92*	3.4	17.33*	10.02**
TAE (n=1)	N/A	2.72	3.88	N/A	11.82	5.71
Systemic therapy						
Octreotide (n=117)	14.5	0.52*	0.57*	51.6	0.57	0.80
Biologic (n=35)	8.9	1.70*	1.48	26.7	1.62	1.35
Cytotoxic (n=54)	8.8	1.70*	1.01	32.9	2.85**	1.72
Prior resection or ablation (n=34)	11.5	1.43	2.16**	32.9	1.28	1.87

* P < 0.05; ** P < 0.005



Conclusions

- TARE demonstrated improved HPFS in grade 1 and 2 tumors, but worse HPFS and OS in grade 3 tumors compared to TACE.
- Higher tumor grade and tumor burden were associated with shorter HPFS and OS.
- Prospective studies are needed to determine the optimal embolotherapy for patients with NET liver metastases.